WHAT IS CLAIMED IS

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1. A method of modifying a selected gene in cells of a human skin at one or more locations which comprises delivering to said cells an effective amount of a composition comprising a chimeric RNA-DNA oligonucleotide and a pharmaceutically acceptable carrier such that the stable genetic modifications are made to the selected gene which result in phenotypic changes at said locations of the human skin wherein the selected gene is naturally expressed in cells of the human skin.

2. The method of claim 1, wherein the stable genetic modification is in an epidermal fragility disorder gene.

3. The method of claim 1, wherein the stable genetic modification is in a keratinization disorder gene.

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4. The method of claim 1, wherein the selected gene is tyrosinase, COL7A1, LAMA3, LAMB3, LAMC2, COL17A1, ITGA6, ITGB4, PLEC1, KRT5, KRT14, PKP1, KRT1, KRT10, KRT9, KRT16, LOR, KRT2e, KRT6a, KRT 16, KRT 17, STS, TGM1, GJB2, GJB3, ATP2A2, DSP, DSG1, HR, hHB1, hHB6, PAX3, TYR, TYRP-1, OCA2, OA1, MITF, HPS, FECH, UROS, URO-D, XPA, XPB, XPC, XPD, XPG, CSB, PTC, STK11/LKB1, PTEN, PTEN, XPB, XPD, WHN, GLA, ATM, ENG, ALK-1, or PPO gene.

5. The method of claim 1, wherein the selected gene is tyrosinase gene.

6. The method of claim 1, wherein the selected gene is COL7A1 gene.

7. The method of claim 1, wherein the selected gene is KRT17 gene.

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8. The method of claim 1, wherein the chimeric RNA-DNA oligonucleotide comprises:

(a) a first string of nucleotides wherein the first string is made of at least four contiguous deoxyribonucleotides flanked on each side by at least nine ribonucleotides; and

(b) a second string of nucleotides that is fully complementary to the first string of nucleotides or is fully complementary to the first string of nucleotides except that the first and second strings have one mismatched base pair in the region corresponding to the deoxyribonucleotides of the first string, wherein the second string has the same number of deoxyribonucleotides as in the first string of nucleotides, and

wherein one or more nucleotides of the chimeric RNA-DNA oligonucleotide are nuclease protected, and wherein the chimeric RNA-DNA oligonucleotide has nucleotides in the first and second strings that are fully complementary to a segment of DNA of the selected gene except that the first string has one mismatching deoxyribonucleotide that defines the site of modification in the selected gene.

9. The method of claim 1, wherein the chimeric RNA-DNA oligonucleotide comprises:

(a) a first string of nucleotides wherein the first string is made of at least 20 ribonucleotides; and

(b) a second string of deoxyribonucleotides having the same number of deoxyribonucleotides as in the first string of nucleotides, wherein the second string is fully complementary to the first string of nucleotides except that the second string has a deoxyribonucleotide that forms a mismatched base pair with the corresponding nucleotide in the first string, and

wherein one or more nucleotides of the chimeric RNA-DNA oligonucleotide are nuclease protected, and wherein the chimeric RNA-DNA oligonucleotide has nucleotides in the first and second strings that are fully complementary to a segment of the two strands of DNA of the selected gene except that the deoxyribonucleotide in the second string also forms a mismatched base pair with the corresponding deoxyribonucleotide in the DNA strand of the selected gene which mismatched base pair defines the site of modification in the selected gene.

10. The method of claim 1, wherein the chimeric RNA-DNA oligonucleotide comprises:

(a) a first string of nucleotides wherein the first string is made of at least four contiguous deoxyribonucleotides flanked on each side by at least nine ribonucleotides; and

(b) a second string of nucleotides that is fully complementary to the first string of nucleotides or is fully complementary to the first string of nucleotides except that the first and second strings have one mismatched base pair in the region corresponding to the deoxyribonucleotides of the first string, wherein the second string has the same number of deoxyribonucleotides as in the first string of nucleotides, and

wherein one or more nucleotides of the chimeric RNA-DNA oligonucleotide are nuclease protected, and wherein the chimeric RNA-DNA oligonucleotide has nucleotides in the first and second strings that are fully complementary to a segment of DNA of the selected gene except that the first and second strings have one, two or four pairs of nucleotide insertions or deletions that defines the site of modification in the selected gene.

11. The method of claim 1, wherein the stable genetic modification is correction of a mutation.

12. The method of claim 11, wherein the mutation is a point mutation or a frame shift mutation.

13. The method of claim 1, wherein the stable genetic modification is generation of a mutation.

14. The method of claim 13, wherein the mutation is a point mutation or a frame shift mutation.

15. The method of claim 13, wherein the mutation is a dominant mutation.

16. The method of claim 1, wherein said phenotypic changes include the correction of a skin disorder.

17. The method of claim 1, wherein said phenotypic changes include the correction of albinism, an epidermal fragility disorder or a keratinization disorder.

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18. A method of modifying a selected gene in cells of an animal skin at one or more locations which comprises delivering to said cells an effective amount of a composition comprising a chimeric RNA-DNA oligonucleotide and a pharmaceutically acceptable carrier such that the stable genetic modifications are made to the selected gene which result in phenotypic changes at said locations of the animal skin, wherein the animal is selected from the group consisting of a mouse, a rabbit, a goat, a monkey, a pig and a cow.

19. The method of claim 17, wherein the selected gene is tyrosinase, COL7A1, LAMA3, LAMB3, LAMC2, COL17A1, ITGA6, ITGB4, PLEC1, KRT5,

KRT14, PKP1, KRT1, KRT10, KRT9, KRT16, LOR, KRT2, KRT6, KRT 16, KRT 17, STS, TGM1, GJB2, GJB3, ATP2A2, DSP, DSG1, HR, hHB1, hHB6, PAX3, TYR, TYRP-1, OCA2, OA1, MITF, HPS, FECH, UROS, URO-D, PPO, XPA, XPB, XPC, XPD, XPG, CSB, PTC, STK11/LKB1, PTEN, PTEN, XPB, XPD, WHN, GLA, ATM, ENG, ALK-1, or a cytokine gene.

20. The method of claim 18, wherein the selected gene is tyrosinase gene.

21. The method of claim 18, wherein the selected gene is COL7A1 gene.

22. The method of claim 18, wherein the selected gene is KRT17 gene.

23. The method of claim 18, wherein the chimeric RNA-DNA oligonucleotide comprises:

(a) a first string of nucleotides wherein the first string is made of at least four contiguous deoxyribonucleotides flanked on each side by at least nine ribonucleotides; and

(b) a second string of nucleotides that is fully complementary to the first string of nucleotides or is fully complementary to the first string of nucleotides except that the first and second strings have one mismatched base pair in the region corresponding to the deoxyribonucleotides of the first string, wherein the second string has the same number of deoxyribonucleotides as in the first string of nucleotides, and

wherein one or more nucleotides of the chimeric RNA-DNA oligonucleotide are nuclease protected, and wherein the chimeric RNA-DNA oligonucleotide has nucleotides in the first and second strings that are fully complementary to a segment of DNA of the selected gene except that the first string has one mismatching deoxyribonucleotide that defines the site of modification in the selected gene.

24. The method of claim 18, wherein the chimeric RNA-DNA oligonucleotide comprises:

(a) a first string of nucleotides wherein the first string is made of at least 20 ribonucleotides; and

(b) a second string of deoxyribonucleotides having the same number of deoxyribonucleotides as in the first string of nucleotides, wherein the second string is fully complementary to the first string of nucleotides except that the second string has a deoxyribonucleotide that forms a mismatched base pair with the corresponding nucleotide in the first string to make the genetic modifications in the selected gene, and

wherein one or more nucleotides of the chimeric RNA-DNA oligonucleotide are nuclease protected, and wherein the chimeric RNA-DNA oligonucleotide has nucleotides in the first and second strings that are fully complementary to a segment of the two strands of DNA of the selected gene except that the deoxyribonucleotide in the second string also forms a mismatched base pair with the corresponding deoxyribonucleotide in the DNA strand of the selected gene which mismatched base pair defines the site of modification in the selected gene.

25. The method of claim 18, wherein the chimeric RNA-DNA oligonucleotide comprises:

(a) a first string of nucleotides wherein the first string is made of at least four contiguous deoxyribonucleotides flanked on each side by at least nine ribonucleotides; and

(b) a second string of nucleotides that is fully complementary to the first string of nucleotides or is fully complementary to the first string of nucleotides except that the first and second strings have one mismatched base pair in the region corresponding to the deoxyribonucleotides of the first string, wherein the second

string has the same number of deoxyribonucleotides as in the first string of nucleotides, and

wherein one or more nucleotides of the chimeric RNA-DNA oligonucleotide are nuclease protected, and wherein the chimeric RNA-DNA oligonucleotide has nucleotides in the first and second strings that are fully complementary to a segment of DNA of the selected gene except that the first and second strings have one, two or four pairs of nucleotide insertions or deletions that defines the site of modification in the selected gene.

26. The method of claim 18, wherein the stable genetic modification is correction of a mutation.

27. The method of claim 26, wherein the mutation is a point mutation or a frame shift mutation.

28. The method of claim 18, wherein the stable genetic modification is generation of a mutation.

29. The method of claim 28, wherein the mutation is a point mutation or a frame shift mutation.

30. The method of claim 28, wherein the mutation is a dominant mutation.

31. The method of claim 18, wherein said phenotypic changes include the correction of albinism, an epidermal fragility disorder or a keratinization disorder.

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32. An animal model having a skin disorder at one or more locations of its skin wherein the skin disorder is a result of a treatment at said locations with a composition comprising a chimeric RNA-DNA oligonucleotide targeted to a selected skin gene, wherein the skin disorder is an epidermal fragility disorder, a keratinization disorder or albinism disorder.

33. The animal model of claim 32, wherein the selected skin gene is Tyr, COL7A1, LAMA3, LAMB3, LAMC2, COL17A1, ITGA6, ITGB4, PLEC1, KRT5, KRT14, PKP1, KRT1, KRT10, KRT9, KRT16, LOR, 1998, KRT2e, KRT6a, KRT 16, KRT 17, STS, TGM1, GJB2, GJB3, ATP2A2, DSP, DSG1, HR, hHB1, hHB6, PAX3, TYR, TYRP-1, OCA2, OA1, MITF, HPS, FECH, UROS, URO-D, PPO, XPA, XPB, XPC, XPD, XPG, CSB, PTC, STK11/LKB1, PTEN, PTEN, XPB, XPD, WHN, GLA, ATM, ENG, ALK-1, or a cytokine gene.

34. The method of claim 33, wherein the selected gene is Tyr gene.

35. The method of claim 33, wherein the selected gene is COL7A1 gene.

36. The method of claim 33, wherein the selected gene is KRT17 gene.

37. The method of claim 32, wherein the skin disorder is due to generation of a mutation in the selected skin gene.

38. The method of claim 37, wherein the mutation is a point mutation or a frame shift mutation.

39. The method of claim 37, wherein the mutation is a dominant mutation.

40. A method of correcting a mutation in a tyrosinase gene in cells of a mammalian skin at one or more locations which comprises delivering to said cells an effective amount of a composition comprising a Tyr-A RNA-DNA oligonucleotide for causing stable genetic correction in the tyrosinase gene and a pharmaceutically acceptable carrier such that the correction results in restoration of tyrosinase enzyme activity at said locations of the mammalian skin, wherein the mammalian skin is selected from the group consisting of a human, a mouse, a rabbit, a goat, a monkey, a pig and a cow.

Table 1. Genodermatoses and genes with known gene defects

Disease	Affected gene	References
Epidermal fragility disorders		
Dystrophic EB	COL7A1	Uitto, et al., 1996, In: Epidermolysis Bullosa: Clinical, Epidemiologic and Laboratory Advances, and the Findings of the National Epidermolysis Bullosa Registry (Fine J-D, Bauer EA, McGuire J, and Moshell A, eds.) The Johns Hopkins University Press, Baltimore, MD, pp. 326-350
Junctional EB	LAMA3, LAMB3, LAMC2	Pulkkinen et al., 1999, In: Epidermolysis Bullosa: Clinical, Epidemiologic and Laboratory Advances, and the Findingi of the National Epidermolysis Bullosa Registry (Fine, J.-D., Bauer, E.A., McGuire, J., and Moshell, A., eds.) The Johns Hopkins University Press, Baltimore, MD, pp. 300-325
GABEB	COL17A1	Pulkkinen et al., 1998, Exp Dermatol 7:46
EB-PA	ITGA6, ITGB4	Pulkkinen et al., 1998, Exp Dermatol 7:46
EB-MD	PLEC1	Uitto et al., 1996, Exp Dermatol 5:237
EB-simplex	KRT5, KRT14	Corden et al., 1996, Exp Dermatol 5:297
EDA/skin fragility	PKP1	McGrath et al., 1997, Nat Genet 17:240
Keratinization disorders		
Epidermolytic hyperkeratosis	KRT1, KRT10	Corden et al., 1996, Exp Dermatol 5:297
Epidermolytic PPK KRT9	Corden et al., 1996, Exp Dermatol 5:297	
Non-epidermolytic PPK	KRT16	Corden et al., 1996, Exp Dermatol 5:297
Vohwinkel's syndrome	LOR	Ishida-Yamamoto et al., 1998, Exp Dermatol 7:1
Ichthyosis bullosa Siemens	KRT2e	Rothnagel JA 1996, Current Op Dermatol 3:127
Pachonychia congenita type 1/2	KRT6a, 16, 17	Rothnagel JA 1996, Current Op Dermatol 3:127
X-linked ichthyosis	STS	Bonifas et al., 1987, Proc Nat Acad Sci 84:9248
Lamellar ichthyosis	TGM1	Ishida-Yamamoto et al., 1998, Exp Dermatol 7:1
Palmoplantar keratoderma with deafness	GJB2	Richard et al., 1998, Hum Genet 103:393
Erythrokeratodermia variabilis	GJB3	Richard et al., 1998, Nat Genet 20:366
Darier's disease	ATP2A2	Sakuntabhai et al., 1999, Nat Genet 21:271
Striate palmoplantar keratoderma	DSP	Armstrong et al., 1999, Hum Molec Genet 8:143
Striate keratoderma	DSG1	Rickman et al., 1999, Hum Mol Genet, (In Press)
Hair disorder		
Congenital atrichia	HR	Ahmad et al., 1998, Science 279:720
Monilethrix	hHB1, hHB6	Korge et al., 1998, J Invest Dermatol 111:896; Winter et al., 1997, Nat Genet 16:372

Disease	Affected gene	References
Pigmentation disorders		
Waardenburg syndrome	PAX3	Nordlund et al., 1998, Oxford Univ Press
Albinism (different forms)	TYR, TYRP-1, OCA2, OA1	Boissy et al., 1997, Pigment Cell Res 10: 12
Tietz syndrome	MITF	Nordlund et al., 1998, Oxford Univ Press
Hermansky-Pudlak syndrome	HPS	Boissy et al., 1997, Pigment Cell Res 10: 12
Porphyrias		
Erythropoietic protoporphyria	FECH	Murphy GM, 1999, Br J Dermatol 140:573
Congenital erythropoietic porphyria	UROS	Murphy GM, 1999, Br J Dermatol 140:573
Familial porphyria cutanea tarda	URO-D	Murphy GM, 1999, Br J Dermatol 140:573
Variegate porphyria	PPO	Murphy GM, 1999, Br J Dermatol 140:573
Cancer disorders		
Xeroderma pigmentosum	XPA, XPB, XPC, XPD, XPG, CSB	van Steeg et al., 1999, Mol Med Today 5:86
Basal cell nevus syndrome	PTC	Bale et al., 1998, J Cutan Med Surg 3:31; Ingham PW, 1998, Curr Opin Genet Dev 8:88
Peutz-Jeghers	STK11/LKB1	Dong et al., 1998, Cancer Res 58:3787; Rowan et al., 1999, J Invest Dermatol 112:509
Cowden syndrome	PTEN	Eng C, 1998, Int J Oncol 12:701
Bannayan-Zonan syndrome	PTEN	Marsh et al., 1997, Nat Genet 16:333
Multisystem disorders		
Trichothiodystrophy	XPB, XPD	van Steeg et al., 1999, Mol Med Today 5:86
Nude	WHN	Frank et al., 1999, Nature 398:473
Fabry's disease	GLA	Peters et al., 1997, Postgrad Med J 73:710
Ataxia telangiectasia	ATM	Crawford TO, 1998, Semin Pediatr Neurol 5:287
Hereditary hemorrhagic telangiectasia (HHT)	ENG, ALK-1	Marchuk DA, 1998, Curr Opin Hematol 5:332

Abbreviations: EB, epidermolysis bullosa; GABEB, generalized atrophic benign EB; PA, pyloric atresia; MD, muscular dystrophy; EDA, ectodermal dysplasia; PPK, palmoplantar keratoderma.